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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/994,622	12/19/97	GILBERT	C 2131020-CIP2

EXAMINER

HM11/1021

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ART UNIT	PAPER NUMBER
1654	8

DATE MAILED: 10/21/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 7-6-1998

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-48 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-9, 11-13, 15-27, and 30-48 is/are rejected.
☒ Claim(s) 10, 14, 28, and 29 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-421-632/40207

In the Office action mailed October 15, 1998, an incorrect form paragraph was used in paragraph 4 of the Office action. The form paragraph has been corrected in this Office action, which otherwise duplicates the contents of the previous Office action. The shortened statutory period for response will be re-set to begin from the date that this Office action is mailed. The examiner regrets any inconvenience this error may cause Applicants.

1. The use of the trademark "TWEEN" has been noted in this application (see page 16, line 27). This trademark should be entirely capitalized and should be accompanied by the generic terminology. See MPEP 608.01(v).

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

2. Claims 40-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no original disclosure of the subject matter recited in claims 40-48 contained in the preliminary amendment filed July 6, 1998, either in the instant specification or in the specification of the parent application incorporated by reference in the instant specification. There is no literal support for the T_{max} ranges of at least about 4 times greater or at least about 8 times greater (see claims 40 and 41). Further, these ranges embrace values of T_{max} significantly greater than 8, and two examples (see Table 6) do not provide support for a range of T_{max} without

any upper limit. Similarly, there is no literal support for the conjugate activity range of at least about 10% of the activity of unmodified alpha-interferon (see claims 45-48). This range embraces activity values significantly greater than the 69% disclosed in Table 5, and three examples do not provide support for an activity range without any upper limit. There is no literal support for a $T_{1/2}$ range of about 5 hours alpha phase. While Table 6 discloses a $T_{1/2}$ alpha phase of 5.8 hours, it is not clear that this value is embraced by the claimed range, and in any event does not constitute disclosure of values, e.g., of less than 5 hours which are also embraced within the range. Finally, the disclosure in the instant and parent specifications which concerns T_{max}, activity, and $T_{1/2}$ is limited to two specific conjugates, 2-PEG-rαIFN-PEG_{5000} and 2-PEG-rαIFN-PEG_{12000}, which is not sufficient to support the entire claimed range of alpha interferon conjugates, not limited to the species and/or size of non-antigenic polymer and not limited to the species of alpha-interferon.

3. Claims 15-18, 27, and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no antecedent basis in the claim for the phrase "said substantially non-antigenic polymer" at claim 15, line 3. Note that line 2 of the claim does not require the polymer to be substantially non-antigenic. Claim 27 is indefinite because it requires a polymer molar excess, but then recites a molar ratio whose lower limit, "about 1" embraces less than molar excesses. It is suggested that "about 1" be changed to "above 1".

4. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the

following is required: Should the claim language of claims 40-48 ultimately be determined to be supported by the original disclosure of the invention (see paragraph 2 above), the claim language will have to be inserted verbatim into the specification.

5. The effective filing date of instant claims 1-48 is deemed to be December 19, 1997, the filing date of the instant application. Claims 1-39 are deemed not to be entitled to the benefit of the filing date of parent application 08/337,567 because the parent application '567, under the test of 35 U.S.C. 112, first paragraph, does not disclose conjugation of a polymer to IFN-α through the sidechain of a histidine residue and does not disclose the reaction pH necessary to achieve such conjugation. Claims 40-48 are deemed not to be entitled to the benefit of the filing date of parent application 08/337,567 because the parent application '567, under the test of 35 U.S.C. 112, first paragraph, does not disclose the claimed subject matter for the reasons set forth in paragraph 2 above. Accordingly, Greenwald et al is available as prior art against the instant claims under 35 U.S.C. 102(e), and the European Patent Application '996 is available as prior art under 35 U.S.C. 102(a).

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 1-9, 11-13, 15-27, and 30-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Greenwald et al. Greenwald et al teach Applicants' claimed method of preparing alpha-interferon conjugates, namely reacting recombinant alpha-interferon-2b with PEG which has been activated with bis-succinimidyl carbonate. The PEG has a molecular weight of about 8,000.

The reaction pH is about 6.5, and the molar ratios of interferon to PEG are about 2:1 and about 1:1. The conjugates are used to treat interferon-susceptible conditions in mammals. See column 3, lines 11-15, and Examples 1-3. Because the reactants and the reaction conditions are the same, inherently at least some of the PEG will be conjugated to the IFN-α through the sidechain of a histidine residue to the same extent claimed by Applicants, and inherently the same mixture of positional isomers will result in Greenwald et al to the same extent claimed by Applicants. The reaction products of Greenwald et al are deemed to be pharmaceutical compositions because they comprise pharmaceutically active ingredients (i.e. reacted and unreacted interferon-alpha) and a pharmaceutically active carrier (i.e. water) and do not contain any toxic components. Note that Applicants' claims merely require of the pharmaceutical compositions that a mixture of positional isomers be present and set forth no other limitations on the compositions.

8. Claims 40-48 are rejected under 35 U.S.C. 102(e) as being anticipated by Greenwald et al. Greenwald et al teach forming an alpha-interferon-PEG conjugate according to the method of US Patent No. 5,122,614. The retained activity of the conjugated compared to unconjugated interferon-alpha is about 30%. See Example 4. This is the same method by which Applicants form their conjugates of Example 10. In view of the similarity in method of making and in retained activity between the conjugate of Greenwald et al and Applicants' claimed conjugates, the former is deemed to anticipate the latter and Applicnats' claimed increases in T_{max}, AUC, and subcutaneous activity and Applicants' claimed alpha phase $T_{1/2}$ is deemed inherent in the product of Greenwald et al. Sufficient evidence of similarity between the conjugate of Greenwald et al

and Applicants' claimed conjugate is deemed to be present to shift the burden to Applicants to provide evidence that their claimed conjugates are unobviously different than the conjugate of Greenwald et al. Note that Greenwald et al need not describe their conjugate using the same terminology chosen by Applicants, e.g. in terms of subcutaneous activity, in order to anticipate Applicants' claimed conjugate.

9. Claims 40-48 are rejected under 35 U.S.C. 102(a) as being anticipated by the European Patent Application '996. The European Patent Application '996 teaches a PEG-IFNα conjugate having an increased half-life, an increased plasma residence time, and an increased subcutaneous activity compared to unconjugated IFNα. See Examples 1, 4, and 6. In view of the similarity in composition and activities between the PEG-IFNα conjugate of the European Patent Application '996 and Applicants' claimed conjugates, the former is deemed to anticipate the latter and the claimed increases in T_{max} and AUC and the claimed alpha phase $T_{1/2}$ is deemed inherent in the product of the European Patent Application '996. Sufficient evidence of similarity between the conjugate of the European Patent Application '996 and Applicants' claimed conjugate is deemed to be present to shift the burden to Applicants to provide evidence that their claimed conjugates are unobviously different than the conjugate of the European Patent Application '996.

10. Claims 10, 14, 28, and 29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 10, 14, 28, and 29 are deemed to be novel and unobvious over Greenwald et al. Greenwald et al do not teach conjugation of mPEG or the

polymers of instant claim 14 at a pH of less than about 7.0, and therefore an inherency argument can not be made against these claims. Greenwald et al teach about equimolar ratios or else molar excesses of interferon, and do not teach or suggest the molar excesses of polymer recited in claims 28 and 29.

The Borukhov et al article is cited as art of interest, but is not deemed to teach or suggest the instant claims. Note that the Borukhov et al article, while modifying histidine residues of IFN-α, does not teach or suggest conjugating polymers at these positions, does not teach or suggest forming a pharmaceutical composition comprising a mixture of positional isomers of IFN-α and polymer conjugates, and does not teach or suggest that an oxycarbonyl-oxy-N-dicarboxamide can be used to modify IFN-α at histidine residues.

Gilbert et al is cited as art of interest, but does not raise any obviousness-type double patenting issues with the instant claims.

Zalipsky (U.S. Patent No. 5,122,614) and Gross et al cited to show the general state of the art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (703) 308-0254. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 305-7939 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.

Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

October 20, 1998